GOODMAN and GILMAN's The Pharmacological Basis of Therapeutics

SEVENTH EDITION

MACMILLAN PUBLISHING COMPANY
New York

COLLIER MACMILLAN CANADA, INC.
Toronto

COLLIER MACMILLAN PUBLISHERS
London

PRINTED IN THE UNITED STATES OF AMERICA

Earlier editions entitled *The Pharmacological Basis of Therapeutics* copyright 1941 and 1955, © copyright 1965, copyright © 1970, and copyright © 1975 by Macmillan Publishing Company. Earlier edition entitled *Goodman and Gilman's The Pharmacological Basis of Therapeutics* copyright © 1980 by Macmillan Publishing Company.

MACMILLAN PUBLISHING COMPANY
866 Third Avenue • New York, N.Y. 10022

COLLIER MACMILLAN CANADA, INC.

COLLIER MACMILLAN PUBLISHERS • London

Library of Congress catalog card number 85-15356

Printing: 4 5 6 7 8 Year: 9 0 1

In this textbook, reference to proprietary names of drugs is ordinarily made only in chapter sections dealing with preparations. Such names are given in SMALL-CAP TYPE, usually immediately following the official or nonproprietary titles. Proprietary names of drugs also appear in the Index.

aneous mutation we
ans by which micro
stance to antibiotics
erapy would, in theo
ns of prevention.
equency of mutatio
resistance to one d
. second drug 10^{-6}
endent mutation to
in a single cell is t
equencies, 10^{-13}.
e of such mutan
tically unlikely. In
method has rece
in the treatment of
e concomitant use
iate agents strikingl
ent of drug resista
lus.

ges of Combinations
. It is important th
and the potential ne
use of combina
agents. The most ob
toxicity from two
selection of microo
nt to antibiotics th
essary, and increase
n addition, as note
antibacterial effe
cteriostatic and bac
en concurrently. Th
antibiotic antagoni
od. Although antag
by another has be
ation *in vitro*, we
al examples are
. notable of these in
eumococcal menin

er and Dowling report
ong patients with pne
vere treated with peni
those patients who re
enicillin and chlortetra
79%. This study was su
eagues (1967), who
al meningitis of multip
llin alone or with the
oramphenicol, and s
e among those treate
hile those treated wit
icantly greater—10.
tween antibiotics is p
it in *most* infections
between two antibio

both agents must be active against the in- microorganism. The addition of a bacterio- to a bactericidal drug frequently results in bacteriostatic effect. In many infections host defenses are adequate, this may still be to tip the balance in favor of the host. host defenses are impaired, as in patients utropenia, or with special infections, such ocarditis and meningitis, the bactericidal ef- y become more important. Certain studies rimental animals and in the clinic support ntention. In animals with *Proteus mirabilis* itis, gentamicin alone and a combination of icin and chloramphenicol are equally effec- preventing death. However, if the animals irradiated and rendered neutropenic, the istic combination of gentamicin and chlor- nicol is much less effective than gentamicin in preventing death (Sande and Overton, In clinical trials in man, the more rapidly cidal combinations of antibiotics have in been more effective than less rapidly bacte- or purely bacteriostatic drugs in the therapy -negative infections in neutropenic patients.

PROPHYLAXIS OF INFECTION ANTIBIOTICS

large percentage (from 30 to 50%) of otics administered in the United are given to *prevent* infection rather to treat established disease. This prac- accounts for some of the most flagrant es of these drugs.

ical studies have demonstrated that are some situations in which chemo- hylaxis is highly effective and others in it is totally without value and may in be deleterious. There are still numer- uations where the attempt to use an- obial compounds to prevent bacterial ons is controversial. *In general, if a effective drug is used to prevent in- by a specific microorganism or to ate infection immediately or soon has become established, then che- phylaxis is frequently successful. On er hand, if the aim of prophylaxis is ent colonization or infection by any microorganisms present in the envi- t of a patient, then prophylaxis usu- ils.*

moprophylaxis has been employed y for three purposes. (1) Prophy- may be utilized to protect healthy per- om acquisition of or invasion by spe- microorganisms to which they are ed. Successful examples of this practice include the following: the use of penicillin G to prevent infection by group-A streptococci; prevention of gonorrhea or syphilis after contact; the intermittent use of trimethoprim-sulfamethoxazole to prevent recurrent urinary tract infections usually caused by *E. coli;* the use of rifampin, minocycline, or sulfadiazine to prevent meningococcal disease. (2) Attempts are often made to prevent secondary bacterial infection in patients who are ill with other diseases. Examples of this form of prophylaxis have been efforts to prevent bacterial infection in patients with measles or in those in coma. Likewise, antibiotics are given to prevent infection in patients on respirators. *This form of "total" chemoprophylaxis is usually unsuccessful.* Resistant microorganisms, especially Enterobacteriaceae and fungi, emerge as pathogens and increase in frequency as prophylaxis is prolonged. Although certain centers have reported a decrease in the incidence of bacterial infections in neutropenic patients given trimethoprim-sulfamethoxazole, increased numbers of fungal infections were noted in some series. The normal microbial flora of the host represents an important defense in the prevention of colonization and infection with these pathogens (Sanders and Sanders, 1984). "Shotgun" chemoprophylaxis disrupts this barrier and may be self-defeating. Elaborate technics involving sterile food, life islands, and nonabsorbable antibiotics have shown modest success in decreasing infections in neutropenic patients with hematological malignancies. (3) Chemoprophylaxis *should* be performed to prevent endocarditis in patients with valvular or other structural lesions of the heart who are undergoing dental, surgical, or other procedures that produce a high incidence of bacteremia. Endocarditis results from the bacterial colonization of the cardiac endothelium, particularly that of cardiac valves. The area of colonization is probably a deposit of fibrin and platelets on a damaged valve associated with areas of turbulent blood flow. The prophylactic use of antibiotics is therefore recommended in patients who have cardiac lesions, such as those produced by rheumatic or congenital heart disease that produce turbulence in blood flow. Any proce-

dure that injures a mucous membrane where there are large numbers of bacteria (such as in the oropharyngeal or gastrointestinal tract) will produce transient bacteremia. Streptococci from the mouth, enterococci from the gastrointestinal or genitourinary tract, and staphylococci from the skin have a propensity to produce endocarditis, and chemoprophylaxis directed against these microorganisms is recommended (Medical Letter, 1984). Therapy should not begin until immediately before the procedure, since prolonged administration of antibiotics can lead to colonization by resistant strains. Criteria have been established for the selection of specific drugs and patients who should receive chemoprophylaxis for various procedures (*see* Chapter 50).

Chemoprophylaxis to prevent wound infections after various surgical procedures has created considerable controversy. There are several well-controlled clinical studies that support the use of prophylactic antimicrobial agents in certain surgical procedures. The first such demonstration was by Bernard and Cole (1964), who showed the effectiveness of prophylactic antibiotics in patients undergoing operations involving the stomach, pancreas, and bowel. Wound infection results when a critical number of bacteria are present in the wound at the time of closure. Several factors determine the size of this critical inoculum, and these include the virulence of the bacteria, the presence of devitalized or poorly vascularized tissue, the presence of a foreign body, and the status of the host. Antimicrobial agents directed against the invading microorganisms may reduce the number of viable bacteria below the critical level and thus prevent infection.

Several factors are important to the effective and judicious use of antibiotics in this situation (Sandusky, 1979). First, antimicrobial activity must be present at the wound site at the time of its closure. This has led to the recommendation that the drug be given immediately preoperatively and, perhaps, intraoperatively. Second, the antibiotic must be active against the most likely contaminating microorganisms. This has prompted the wide use of first-generation cephalosporins in this form of chemoprophylaxis. Third, there is mounting evidence that the continued use of drugs after the surgical procedure is *unwarranted*. There are no data to suggest that the incidence of wound infections is lower if antimicrobial treatment is continued after the day of surgery (Rowlands *et al.*, 1982). Prolongation of use beyond 24 to 72 hours does, however, lead to the development of a more resistant flora and of wound infections caused by antibiotic-resistant strains. The risk of toxicity and unnecessary expense are, of course, additional disadvantages. In practice, however, this guideline is frequently broken. In a survey of the usage of antibiotics in Pennsylvania, where one third of all antimicrobial agents used were given for chemoprophylaxis, the median duration of such use was 7 days.

Chemoprophylaxis should be used onl in selected operative procedures. A numbe of studies indicate that it can be justified i dirty and contaminated surgical procedure (*e.g.*, resection of the colon), where the in cidence of wound infections is high. Thes include less than 10% of all operations. I clean surgical procedures, which accour for approximately 75% of the total, the ex pected incidence of wound infection is les than 5%, and antibiotics should not be use routinely. Exceptions are rational when th surgical procedure involves insertion of prosthetic implant. Although clear-cut da are not available to support the use of ant biotics during placement of prosthetic ca diac valves or artificial orthopedic device the complications of infection are so drast that most authorities currently agree wi this indication. Of course, the use of sy temic antibiotics for chemoprophylax during surgical procedures does not redu the need for clean and skilled surgic technic.

SUPERINFECTIONS CAUSED BY ANTIMICROBIAL AGENTS

The untoward reactions produced anti-infective agents include toxic effe and hypersensitivity reactions. These a discussed for individual agents in the cha ters that follow. Antibiotics also ca unique reactions that result from alteratio in the microbial flora of the host.